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Synergistic Interactions of Insufficient Physical Activity and a High Systemic Immune-Inflammation Index on Psychological Problems in Indonesians With Type 2 Diabetes Mellitus

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Abstract

Background: High-grade inflammation represents a critical contribution to the onset of depression and might be manageable by physical activity (PA). Nevertheless, no study has examined synergistic interactions of insufficient PA and high values of the systemic immune-inflammation index (SII) on psychological problems. **Objective:** We investigated independent and synergistic interactions of insufficient PA and high SII levels on stress, anxiety, and depression in T2DM patients. **Methods:** A cross-sectional research design with 294 T2DM patients was conducted. An XP-100 automated hematology analyzer was used to evaluate inflammatory biomarkers. Depression, Anxiety, and Stress Scale-21 items and a standardized questionnaire about PA were respectively used to measure psychological problems and metabolic equivalent of task (MET)-h/week. **Results:** A multiple linear regression demonstrated that patients with insufficient PA were significantly more likely to have higher stress (β = 1.84, 95% confidence interval (CI) = 1.03–2.65), anxiety (β = 1.88, 95% CI = 1.81–2.96), and depression (β = 2.53, 95% CI = 0.82–4.24) than those with active PA. A high SII level was a key predictor and was most strongly associated with stress (β = 2.61, 95% CI = 2.02–3.20), anxiety (β = 3.16, 95% CI = 2.37–3.94), and depression (β = 3.72, 95% CI = 2.49–4.96) compared to those who had low SII levels. Notably, additive interaction results showed that combining insufficient PA and a high SII level had a significantly escalated 1.7-fold risk of stress, 1.82-fold risk of anxiety, and 2.69-fold risk of depression. **Conclusions:** Active PA and a low SII had a positive synergistic effect of decreasing psychological problems.

Keywords
anxiety, depression, type 2 diabetes mellitus, stress, physical activity, systemic immune-inflammation index

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Introduction

Type 2 diabetes mellitus (T2DM) and psychological problems are recognized as requiring attention (Alzahrani et al., 2019; Kalra et al., 2018). Psychological problems among T2DM patients, such as stress, anxiety, and depression, were identified as crucially influential on the quality of life (McCoy & Theeke, 2019). Individuals with T2DM are roughly twice as likely as those without the disease to suffer from depression (Darwish et al., 2018). Moreover, a previous meta-analysis study revealed that approximately 14.5% (Wang et al., 2019) and 14% (Grigsby et al., 2002) of individuals with T2DM globally have depression and anxiety symptoms, respectively. Early recognition and routine screening for psychological problems may improve control of glucose levels and alleviate stress and anxiety in individuals with T2DM (Kalra et al., 2018; Young-Hyman et al., 2016). Interestingly, in Indonesia, there is a lack of epidemiological studies that specifically examined the potential link between psychological problems and T2DM-determining factors (Nasirin & Lionardo, 2020; Rias, Kurniasari, et al., 2020). Thus, an investigation of the vulnerability to stress, anxiety, and depression among Indonesians with T2DM also needs to be conducted.

Physical activity (PA) may be crucial for reducing psychological problems, given that diabetes has also been linked to poorer mental health (Rebar et al., 2015; White et al., 2017). PA was correlated with a 2.90-fold reduction in depression, which indicates that PA may help ameliorate depression among individuals with T2DM (Narita et al., 2019). A study in Saudi Arabia revealed that individuals with insufficient PA had a 2.77-fold risk of having anxiety compared to those with active PA (AlBekairy et al., 2017). Individuals who had insufficient PA were significantly associated with having diabetes distress (Tran et al., 2020). Regrettably, there is a lack of research examining PA and psychological problems, including depression, anxiety, and stress, in individuals with T2DM, especially in Indonesia. Consequently, estimates of how promoting PA affects declines in depression, anxiety, and stress among T2DM patients in Indonesia must be determined.

A review study demonstrated that the neutrophil-lymphocyte ratio (NLR) and the systemic immune-inflammation index (SII) are reproducible tests for detecting the level of inflammatory abnormalities and are closely associated with depression among persons with diabetes (Wang et al., 2021). The SII is a new and integrated prognostic marker for inflammation that is calculated by multiplying the platelet count by the NLR count (Walzik et al., 2021). A study in the USA demonstrated that persons with a high level of NLR had a 1.57-fold risk of depression (Wang et al., 2020) and a high level of the SII was a risk factor for depression among individuals with T2DM (Wang et al., 2021). Nonetheless, few studies have explored the role of the NLR and SII in relation to depression among persons with diabetes (Wang et al., 2020, 2021). Moreover, no study examined correlations of the NLR and SII with stress and anxiety among T2DM patients. Thus, relationships between inflammation markers, including the NLR and SII, with stress, anxiety, and depression among individuals with T2DM need further investigation.

Remarkably, a randomized-controlled trial suggested that participants with active PA were significantly correlated with a low level of the SII (Winker et al., 2022). PA (Loprinzi et al., 2013) and a low level of the SII (Wang et al., 2021) were inversely correlated with depressive symptoms among individuals with T2DM. In view of the above, possible mechanisms for the synergistic interaction on stress, anxiety, and depression might be clarified by examining correlations between insufficient PA and inflammatory markers such as the SII and NLR. Consequently, we further hypothesized that the synergistic effect of a PA-induced decrease in the SII underlies the anti-inflammatory mechanism and may attenuate levels of psychological problems. Interestingly, the role of the synergistic effect of insufficient PA with the SII in T2DM-related stress, anxiety, and depression remains questionable. We further hypothesized that independent and synergistic effects of insufficient PA and a high level of the SII would be associated with T2DM-psychological problems among the Indonesian population.

Methods

Study Design

This was a cross-sectional study with stratified multistage cluster sampling in East Java Province, Indonesia. In the first phase, we conveniently chose East Java as one of Indonesia's provinces with the highest incidence of T2DM and stratified it into 38 regions. In the second phase, four regions encompassing rural and urban areas were selected by convenience sampling. In the third phase, eight community clinics were randomly selected from four regions. However, three community clinics declined to participate. In the final phase, the eligibility of participants was selected by convenience sampling from five community clinics in East Java Province (Figure 1). The study protocol ERC-009/KET-TPEP/X was confirmed by the Siti Khodijah Muhammadiyah Sepanjang Hospital Ethical Review Broad and was in compliance with the *Declaration of Helsinki*. Each participant provided written or verbal consent after receiving information regarding the research. In addition, the study protocol adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) cross-sectional study reporting guidelines.

Study Participants

Inclusion criteria for participants were as follows: (1) self-reported Indonesian nationality; (2) aged 17–79 years; (3) with a physician-confirmed diagnosis of T2DM with plasma glucose levels of ≥200 mg/dL 2 h after eating or a fasting plasma glucose level of >126 mg/dL (American Diabetes Association, 2018); and

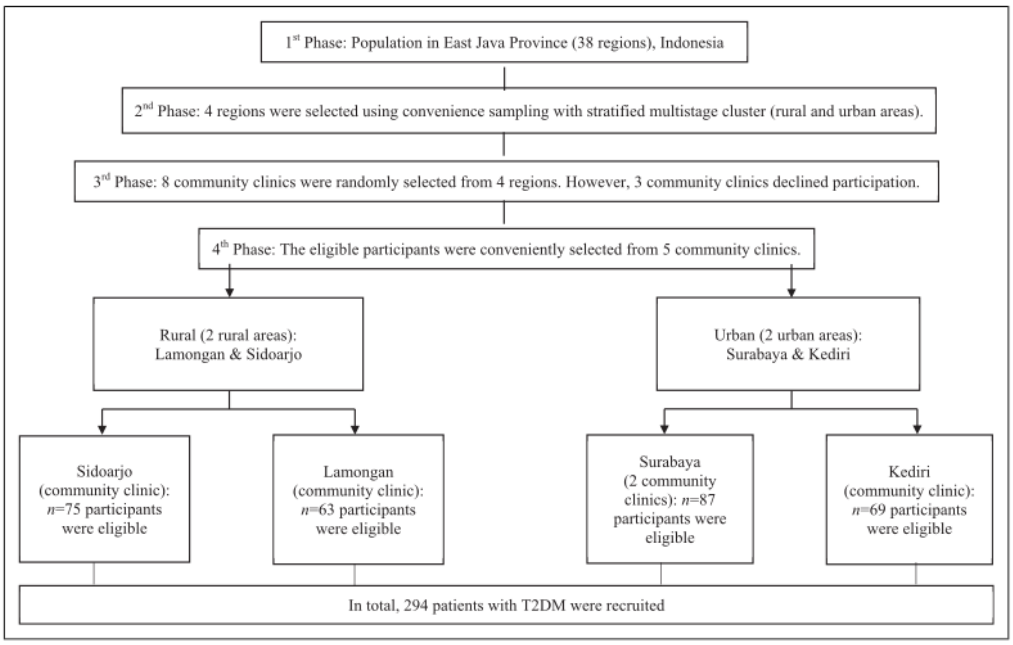

Figure 1. Study sample flowchart.

(4) attendance at one of five community clinics that collaborated and were willing to participate. Participants who (1) were pregnant; (2) used antidepressants; (3) had severe cognitive problems (e.g., dementia or language deficits); or (4) had a disability, were excluded from our research.

Sample Size Calculation

Total participants were calculated with sample size software, G-Power vers. 3.1. An a priori type of power analysis and F-test with a linear multiple-regression test presented the input parameters including Cohen's effect size (f^2) of 0.12 (Salinero-Fort et al., 2018), an α error probability of 0.01, power (1-ß error probability) of 0.90, and number of predictors of 11 predictor variables. The sample size was calculated to be approximately 245 participants. To optimize the study's power and minimize the covariance of parameters and the margin of error, we considered enhancing the final sample size by up to 20% to 294.

Data Collection

Demographic characteristics. All demographic information was collected by trained nursing professionals using a standard questionnaire that contained questions concerning participant demographics including age, income, gender, education, marital status, smoking status, and duration of diabetes. The validity and reliability of the questionnaire demographics were documented in a previous investigation (Budiarti et al., 2018).

Physical examination and biochemical measurements. Biochemical and physical examinations were conducted using the body-mass index (BMI) and a fasting blood sample. Research assistants were responsible for taking the height (m^2) and body weight (kg) measurements to calculate the BMI, categorized as non-obese with a BMI of <25 kg/m^2 and obese with a BMI of ≥25 kg/m^2 (World Health Organization, 2004). Moreover, a BMI of ≥25 kg/m^2 was used as a cutoff of obesity based on the Asia-Pacific-specific cutoff point of obesity (World Health Organization, 2000). The SII and NLR measurements obtained from fasting blood samples were calculated from absolute platelet, neutrophil, and lymphocyte counts. The NLR was defined as the neutrophil count divided by the lymphocyte count and classified as "low level" if a participant scored <1.940 or "high level" if a participant scored ≥1.940 as justified by the area under the curve (AUC) of 0.828, with 80% for both the sensitivity and specificity. We also calculated the SII by multiplying the platelet count by the NLR count and defined the measure as <585.88 (low level) or ≥585.88 (high level) following an AUC score of 0.860, with 83% sensitivity and 90% specificity.

Assessment of psychological problems. The Depression, Anxiety, and Stress Scale-21 items (DASS-21) questionnaire was utilized to evaluate psychological problems including stress,

anxiety, and depression (Lovibond & Lovibond, 2013). Each item was assigned a value with a 4-point Likert scale of 0–3, and the total score ranged 0 to 63. In this study, the DASS-21 total for each domain score was classified as a score of ≥10 for depression, a score of ≥8 for anxiety, and a score of ≥15 for stress symptoms. Cronbach's alpha values for depression, anxiety, and stress in the Indonesian version were 0.86, 0.81, and 0.78, respectively (Oei et al., 2013). In our study, Cronbach's alpha values for depression, anxiety, and stress were 0.93, 0.87, and 0.82, respectively.

Assessment of physical activity (PA). The PA level was determined using three questions regarding modified PA guidelines from the Godin Leisure-Time Exercise questionnaire (GLTEQ) and Advisory Committee for Americans by calculating the metabolic equivalent of task (MET)-h/week (Godin & Shephard, 1997; Rias, Kurniasari, et al., 2020; Wen et al., 2011). Participants were required to report the type, duration in minutes, and intensity of exercise they performed during a typical 7-day period, with exercise types divided into the following categories of light exercise (easy walking, fishing from the riverbank, cleaning the floor), moderate exercise (easy bicycling, fast walking, swimming), and vigorous exercise (football, squash, jogging). The participant's total MET-h/week was calculated by multiplying the number of hours and intensity spent at each PA level by three for light, five for moderate, and nine for vigorous. MET-h/week was categorized into five levels: inactive (<3.75 MET-h/week) and low (3.75–7.49 MET-h/week), moderate (7.50–16.49 MET-h/week), high (16.50–25.49 MET-h/week), and very high (≥25.50 MET-h/week) levels of physical activity per week (Rias, Kurniasari, et al., 2020; Wen et al., 2011). In our study, we classified the total MET-h/week as a score of ≥7.5 MET-h/week for active PA, and a score of <7.5 MET-h/week for insufficient PA (Rias, Gordon, et al., 2020). In fact, meeting the 2008 PA guidelines for Americans proved that engaging in ≥150 min of moderate-to-vigorous PA (equivalent to ≥7.5 MET-h/week) was beneficial and recommended (Arem et al., 2015). Total weekly PA was calculated in arbitrary units by summing the products of the different exercise patterns as described below. For instance, if a respondent had 60 min of easy walking (light) 4 times/week, 60 min easy bicycling (moderate) 2 times/week, and played 30 min of squash (vigorous) one time/week, the weekly total MET-h/week score was (3 [light] × 1 h/time × 4 times/week) + (5 [moderate] × 1 h/time × 2 times/week) + (9 [vigorous] × 0.5 h/time × 1 times/week) = 12 + 10 + 4.5= 16.5 MET-h/week (score ≥7.5 MET-h/week for active PA).

Data Analysis

Statistical analyses were calculated using the SPSS statistical package (vers. 25.0, Chicago, IL, USA). We provide continuous data as the mean (standard deviation (SD) and categorical data as the frequency (*n*) and percentage (%). Our data had a Z-score for skewness and kurtosis of <3.29 which confirmed a normal distribution (Kim, 2013). Moreover, our data presented low multicollinearity with a maximum variance inflation factor value of 2.01. To examine differences among demographic characteristics, determinant factors, and outcomes, an independent *t*-test and Pearson's correlation were performed. Multiple linear regression involves adjusted ß coefficients (adjusted odds ratios (aORs) and 95% confidence intervals (CIs) which were constructed to examine variables that had independent relationships with stress, anxiety, and depression after adjusting for confounding variables. The additivity interaction between PA and the SII on psychological problems was evaluated after constructing four dummy variables as follows; (1) both active PA and low SII (reference condition or ßa); (2) both insufficient PA and a low SII (ßb); (3) both active PA and a high SII (ßc); and (4) both insufficient PA and a high SII (ßd). Thus, we calculated it following the formulae (1) ißd = ßc + ßb indicated no interaction; (2) ßd < ßc + ßb indicated a negative interaction; and (3) ßd > ßc + ßb indicated a positive interaction (Knol et al., 2007). Additionally, we simultaneously assessed the linear regression for interaction additivity to adjust for confounding variables.

Results

Table 1 shows differences between demographic distributions and physical problems in individuals with T2DM. In total, 294 respondents completed the survey, of whom 237 (80.6%) were female, and the largest income status group was low income ($n = 255$, 86.7%). Only gender differences were significant for stress, anxiety, and depression. We found a significant difference by age, marital status, and income for depression, but no significant differences in stress or anxiety.

Table 2 shows substantial differences in determinant factors with stress, anxiety, and depression in participants with T2DM. We found no significant differences in the duration of the disease in stress and anxiety but a significant difference in depression. Generally, mean (SD) stress, anxiety, and depression levels were significantly higher in respondents with a BMI of ≥25 kg/m^2, with insufficient PA, and who were active smokers. More than half, 63.3% and 62.6%, of respondents had high levels of the NLR and SII, respectively.

Table 3 shows results of the multiple linear regression analysis which revealed that respondents with insufficient PA were significantly more likely to have higher stress ($\beta = 84$, 95% CI = .3 to 2.65), anxiety ($\beta = 1.88$, 95% CI = 1.81–2.96), and depression ($\beta = 2.53$, 95% CI = 0.82–4.24) compared to those with active PA levels. Compared to respondents with a low NLR level, respondents with a high NLR level were respectively 1.20-, 1.66-, and 1.59-times more likely to have stress, anxiety, and depression. Importantly, a high SII level was a key predictor and was most strongly associated with stress ($\beta = 2.61$, 95% CI = 2.02–3.20), anxiety ($\beta = 3.16$, 95% CI = 2.37–3.94), and depression ($\beta = 3.72$, 95% CI = 2.49–4.96) compared to those who had a low SII level after adjusting for confounding variables. Respondent's age, gender,

Table 1. Associations Between Demographic Distributions and Psychological Problems in Individuals with Type 2 Diabetes Mellitus (n = 294).

Characteristic	Total Participants (n = 294) n (%)	DASS-21 Stress Mean (SD)	p value	DASS-21 Anxiety Mean (SD)	p value	DASS-21 Depression Mean (SD)	p value
Age (years)							
<55	146 (49.7)	14.20 (2.53)	0.633	10.50 (3.25)	0.369	13.99 (4.27)	0.039
≥55	148 (50.3)	14.34 (2.47)		10.16 (3.18)		12.87 (4.92)	
Gender							
Male	57 (19.4)	15.11 (2.43)	0.005	11.05 (2.71)	0.034	14.72 (4.14)	0.019
Female	237 (80.6)	14.07 (2.48)		10.16 (3.31)		13.11 (4.70)	
Education							
ISCED ≥3	125 (42.5)	14.41 (2.40)	0.412	10.33 (3.25)	0.993	13.40 (4.28)	0.936
ISCED <3	169 (57.5)	14.17 (2.57)		10.33 (3.20)		13.44 (4.89)	
Marital status							
Not married	159 (54.1)	14.20 (2.61)	0.616	10.45 (3.24)	0.478	13.99 (4.72)	0.024
Married	135 (45.9)	14.35 (2.36)		10.19 (3.19)		12.76 (4.46)	
Income (IDR)							
High income	39 (13.3)	13.72 (2.24)	0.139	9.49 (3.00)	0.079	11.59 (4.08)	0.008
Low income	255 (86.7)	14.35 (2.53)		19.46 (3.23)		13.71 (4.66)	

Note. Independent t -test. DASS-21 = Depression, Anxiety, and Stress Scales; IDR = Indonesian Rupiah rate; ISCED = International Standard Classification of Education; SD = standard deviation. Low income was defined as being below the regional minimum salary.

Table 2. Determinant Factors and Psychological Problems in Individuals with Type 2 Diabetes Mellitus (n = 294).

Characteristic	Total Participants (n = 294) n (%)	DASS-21 Stress Mean (SD)	p value	DASS-21 Anxiety Mean (SD)	p value	DASS-21 Depression Mean (SD)	p value
BMI (kg/m^2)[a]							
<25	178 (60.5)	13.80 (2.50)	<0.001	9.74 (3.16)	<0.001	12.58 (4.83)	<0.001
≥25	116 (39.5)	14.98 (2.33)		11.23 (3.10)		14.72 (4.00)	
Physical activity (MET-h/week)[a]							
≥7.5	21 (7.1)	11.90 (2.61)	<0.001	7.95 (2.36)	<0.001	10.71 (3.18)	0.001
<7.5	273 (92.9)	14.45 (2.40)		10.51 (3.21)		13.63 (4.67)	
Smoking status[a]							
Non-smoker	261 (88.8)	14.10 (2.50)	<0.001	10.12 (3.25)	<0.001	13.21 (4.65)	0.018
Active smoker	33 (11.2)	15.64 (2.04)		12.00 (2.40)		15.12 (4.16)	
NLR[a]							
<1.940	108 (36.7)	12.43 (1.63)	<0.001	7.94 (1.81)	<0.001	10.56 (4.48)	<0.001
≥1.940	186 (63.3)	15.34 (2.28)		11.72 (3.04)		15.09 (3.85)	
SII[a]							
<585.88	110 (37.4)	12.13 (1.36)	<0.001	7.62 (1.56)	<0.001	10.11 (4.09)	<0.001
≥585.88	184 (62.6)	15.55 (2.12)		11.95 (2.83)		15.41 (3.72)	
Duration of diabetes (years)[b]	294 (100)	0.057	0.326	0.093	0.112	0.222	<0.001

Note. [a] Independent t-test; [b] Pearson's correlation. Body-mass index (BMI) of <25 kg/m^2 indicates non-obese and ≥25 kg/m^2 indicates obese; metabolic equivalent of task (MET)-h/week of <7.5 indicates insufficient physical activity and MET-h/week ≥7.5 indicates active physical activity; neutrophil-lymphocyte ratio (NLR) of <1.940 indicates a low level and ≥1.940 indicates a high level; systemic immune-inflammation index (SII) of <585.88 indicates a low level and ≥585.88 indicates a high level. DASS-21 = Depression, Anxiety, and Stress Scales; IDR = Indonesian Rupiah; ISCED = International Standard Classification of Education; SD = standard deviation.

marital status, income, education, duration of disease, BMI, and smoking status were designated as confounding variables for the multiple linear regression.

Table 4 demonstrates additive synergistic interactions of PA and the SII on stress, anxiety, and stress in respondents with T2DM. Respondents with both insufficient PA and a low SII had a significantly escalated 1.71-fold risk of stress, a 1.82-fold risk of anxiety, and a 2.69-fold risk of depression compared to those with both active PA and a low SII after adjusting for confounding variables such as age, gender, marital status,

Table 3. Multiple Linear Regression Analysis of Physical Activity Status, Neutrophil-Lymphocyte Ratio (NLR), Systemic Immune-Inflammation Index (SII), and Psychological Problems in Participants with Type 2 Diabetes Mellitus (n = 294).

	DASS-21 Stress		DASS-21 Anxiety		DASS-21 Depression	
Characteristics	Unadjusted Coef. β (95% CI)	Adjusted Coef. β (95% CI)	Unadjusted Coef. β (95% CI)	Adjusted Coef. β (95% CI)	Unadjusted Coef. β (95% CI)	Adjusted Coef. β (95% CI)
Physical activity (MET-h/week)[a]						
≥7.5	Ref	Ref	Ref	Ref	Ref	Ref
<7.5	2.55 (1.47~3.62) **	1.84 (1.03~2.65) **	2.56 (1.12~3.97) **	1.88 (0.81~2.96) **	2.92 (0.88~4.96) *	2.53 (0.82~4.24) *
NLR[a]						
<1.940	Ref	Ref	Ref	Ref	Ref	Ref
≥1.940	2.91 (2.42~3.41) **	1.20 (0.60~1.79) **	3.77 (3.14~4.40) **	1.66 (0.87~2.45) **	4.53 (3.56~5.51) **	1.59 (0.34~2.85) *
SII[a]						
<585.88	Ref	Ref	Ref	Ref	Ref	Ref
≥585.88	3.42 (2.98~3.87) **	2.61 (2.02~3.20) **	4.33 (3.75~4.91) **	3.16 (2.37~3.94) **	5.30 (4.38~6.22) **	3.72 (2.49~4.96) **

Note. *p < 0.05; **p < 0.001. Metabolic equivalent of task (MET)-h/week of <7.5 indicates insufficient physical activity, and MET-h/week of ≥7.5 indicates a good level of physical activity; NLR of <1.940 indicates a low level and ≥1.940 indicates a high level; SII of <585.88 indicates a low level and ≥585.88 indicates a high level. Adjusted β coefficients and 95% confidence intervals (CIs) were estimated using multiple linear regression after adjusting for age, gender, marital status, income, education, duration of diabetes, body-mass index, and smoking status. DASS-21 = Depression, Anxiety, and Stress Scales; SD = standard deviation.

Table 4. Synergistic Interactions of Physical Activity Levels and the Systemic Immune-Inflammation Index (SII) on Psychological Problems in Patients with Type 2 Diabetes Mellitus (*n* = 294).

	DASS-21 Stress		DASS-21 Anxiety		DASS-21 Depression	
Characteristics	Unadjusted Coef. β (95% CI)	Adjusted Coef. β (95% CI)	Unadjusted Coef. β (95% CI)	Adjusted Coef. β (95% CI)	Unadjusted Coef. β (95% CI)	Adjusted Coef. β (95% CI)
Both MET-h/week of ≥7.5 and SII of <585.88	Ref	Ref	Ref	Ref	Ref	Ref
Both MET-h/week of <7.5 and SII of <585.88	1.69 (0.57~2.81) *	1.71 (0.61~2.81) *	1.49 (−0.07~3.05)	1.82 (0.29~3.34) *	1.65 (−0.79~4.09)	2.69 (0.34~5.05) *
Both MET-h/week of ≥7.5 and SII of ≥585.88	2.68 (1.21~4.15) **	2.33 (0.87~3.80) *	3.16 (1.10~5.21) *	2.39 (0.36~4.41) *	4.23 (1.01~7.44) *	3.31 (0.18~6.44) *
Both MET-h/week of <7.5 and SII of ≥585.88	5.24 (4.14~6.33) **	4.70 (3.58~5.82) **	5.76 (4.23~7.29) **	4.95 (3.40~6.51) **	7.12 (4.72~9.51) **	6.77 (4.37~8.16) **

Note. *$p < 0.05$; **$p < 0.001$. Metabolic equivalent of task (MET)-h/week of <7.5 indicates insufficient physical activity and MET-h/week of ≥7.5 indicates a good level of physical activity; SII of <585.88 indicates a low level and ≥585.88 indicates a high level. Adjusted for age, gender, marital status, income, education, duration of diabetes, body-mass index, smoking status, and the neutrophil-lymphocyte ratio. DASS-21 = Depression, Anxiety, and Stress Scales; SD = standard deviation, SII = systemic immune-inflammation index.

income, education, duration of disease, BMI, smoking status, and NLR levels. Moreover, respondents with both active PA and a high SII level had significantly increased stress, anxiety, and depression scores compared to those with both active PA and a low SII. Our results showed that there were significantly additive interactions from the synergism of both insufficient PA and a high SII level for stress (4.70 > 2.33 + 1.71), anxiety (4.95 > 2.39 + 1.82), and depression (6.77 > 3.31 + 2.69).

Discussion

To the best of the authors' knowledge, this is the first study to demonstrate relationships between insufficient PA and high SII levels for stress, anxiety, and depression in T2DM patients. Our findings indicate that high SII levels and insufficient PA among T2DM patients independently and synergistically had significant additive interactions with escalated stress, anxiety, and depression compared to those with active PA and low SII levels.

Prior research demonstrated a correlation between low levels of PA and depression (Narita et al., 2019). In line with our findings, a previous study revealed that American individuals with T2DM who had moderate to vigorous PA levels had a 1.19-fold reduced risk of depression (Loprinzi et al., 2013). A previous study presented that PA had a significant negative association with anxiety ($r = -0.25, p = 0.04$) among individuals in India with T2DM (Balhara & Sagar, 2011). Therefore, based on findings of a multivariate logistic regression analysis from a prior study, insufficient PA is positively associated with distress among person with diabetes (Alzughbi et al., 2020; Tran et al., 2020). Several biochemical mechanisms might explain the pathways linking PA and psychological problems. First, PA was demonstrated to enhance monoamine neurotransmission in the brain, which reduces mood problems such as depression and anxiety (Hallgren et al., 2020). Second, PA appears to control the hypothalamic-pituitary-adrenal axis, resulting in decreased glucocorticoid levels. Consequently, it reduces stress (Portugal et al., 2013). Third, the protective effect of PA was strongly correlated with escalated neurotransmitters, including beta-endorphins. Increased beta-endorphin production was closely related to the production of analgesia, indicating an improved sense of well-being and mood (Shrihari, 2018).

Another important outcome of the present study was that inflammation markers, including the NLR and SII, were strongly connected to stress, anxiety, and depression. This is in line with a previous study which revealed that in individuals with T2DM, higher levels of the NLR were independently related to a higher likelihood of clinically meaningful depressive symptoms compared to low levels of the NLR (Wang et al., 2020). Individuals with T2DM with a high level of SII had a 1.35-fold increased likelihood of enhanced depression (Wang et al., 2021). Nonetheless, no study has evaluated relationships of SII and the NLR with anxiety and stress among individuals with T2DM. A previous study revealed that the NLR had a strong correlation with anxiety in gastric cancer patients with preoperative treatment (Xu et al., 2016) and stress in multiple sclerosis patients (Al-Hussain et al., 2017). A recent study showed significant differences in the NLR and SII between individuals with depression and those without depression as well as those with and without anxiety, which indicated that anxiety and depression were found to have strong correlations with both the NLR and SII in patients who survived

coronavirus disease 2019 (COVID-19) (Demiryürek et al., 2022). Wang et al. (2021) also reported that after adjusting for any potential confounding factors, the SII and NLR were still both related to depression. Interestingly, the SII posed the most significant threat to depression (Wang et al., 2021). There are several appropriate reasons and mechanisms for understanding that the SII was found to be positively correlated with depression compared to the NLR. First, the SII involves three different types of immune-inflammatory cells, whereas the NLR involves only two types (Wang et al., 2021). Second, the SII is an objective marker of the equilibrium between a host's systemic inflammation and the immune response status. It does this by taking into account neutrophils, platelets, and lymphocytes, all of which are engaged in various pathways of the immunological/inflammatory response (Huang et al., 2019; Mazza et al., 2020). Third, the SII accurately reflects clinical manifestations of the integrated immune-inflammation reaction such as decreased expressions of hippocampal brain-derived neurotrophic factors associated with mental health (Hu et al., 2021; Wei et al., 2022).

Interestingly, our results further showed that the combination of an insufficient PA and a high SII synergistically escalated stress, anxiety, and depression compared to the combination of active PA and a low SII. The potential mechanisms for the synergistic interactions on psychological problems may be explained by the correlation between the SII and PA. Winker et al. (2022) revealed that PA for 45–60 min over 8 weeks was associated with a low level of the SII (Winker et al., 2022). Additionally, previous evidence showed that a higher SII was correlated with depression (Wang et al., 2021). Moreover, higher PA sufficiency among T2DM patients efficiently maintained their lipid concentrations and controlled low levels of inflammatory markers, hence minimized the chance of T2DM patients of developing dyslipidemia and hyperglycemia (Tangvarasittichai, 2015). Remarkably, managing hyperglycemia in these patients can avoid or even prevent complications, ultimately contributing to improved mental health (Black et al., 2018).

The present study has several limitations. Even though our investigation controlled for a substantial number of possible confounding variables, it is probable that we missed other confounding factors. Future research should examine biomarkers of additional pathways, including oxidative stress biomarkers, among T2DM patients. Our study was cross-sectional, and therefore the associations observed cannot be used to draw causal conclusions. In addition, it would be beneficial for future nursing research and practice to include a large cluster multisite study on this topic to establish more-thorough evidence.

Conclusions

The current study demonstrated that levels of active PA and low inflammatory markers such as the SII and NLR were independently related to an increased risk of stress, anxiety, and depression in T2DM patients. Intriguingly, the combination of insufficient PA and a high SII level exhibited a favorable synergistic effect on the risk of psychological problems in Indonesian patients with T2DM. These findings imply that increasing or maintaining active PA and avoiding high SII levels are possibly beneficial for minimizing stress, anxiety, and depression among T2DM patients. This information should be useful for health professionals to recognize treatment-targeted interventions.

Declaration of Conflicting Interests.

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Data Availability.

Our datasets generated during the current research are available from the corresponding author on reasonable request.

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